reported to be conserved in HTLV-1 provirus, and PCR for this region was used to measure total PVL.[23,25] Ohshima *et al.*[25] reported that variation of DNA sequence is frequently detected in the *gag* region of HTLV-1 provirus in patients with ATL. Kamihira *et al.*[24] also reported that most of deficient provirus in patients with ATL lacked part of the *gag* region in the proviral regions of HTLV-1 tested. HTLV-1 provirus with deletion of the 5′LTR, and its flanking internal sequences was also found in patients with ATL.[26] In our study, therefore, we tried to find provirus with deficiencies and/or polymorphism of DNA sequence in the asymptomatic carriers by measuring PVLs for the *gag* and 5′LTR-*gag* regions as ratios to *pX* region PVLs. As a result, median 5′LTR-*gag* PVL/*pX* PVL and *gag* PVL/*pX* PVL ratios of 161 HTLV-1 carriers with relatively high *pX* PVL (equal to or greater than one copy per 100 PBMCs) were 0.97 and 0.61, respectively. Our interpretation of this result was that many HTLV-1 infected cells in asymptomatic carriers harbor provirus with deficiency and/or polymorphism of DNA sequences for the sites of primers and/or probe for *gag* real time-PCR.

Long PCR analysis was performed on 17 carriers with low *gag* PVL/*pX* PVL ratios. Five of 17 carriers (29%) were shown to have the provirus with large deletions of internal DNA sequence including the *gag* region. The clonal expansion of HTLV-1 infected cells harboring defective provirus in these five carriers was most likely. In fact, clonal expansion of HTLV-1 infected cells in C1 was already shown in our previous study.[19] The reason for the low *gag* PVL/*pX* PVL ratios in the other 12 carriers was not clear. Contribution of the sum total of HTLV-1 infected cells with defective provirus, which did not reveal dense bands, was possible. Alternatively, polymorphism of the proviral DNA sequence for the *gag* region may have decreased the efficiency of real time-PCR for *gag* PVL. However, cloning and DNA sequencing of the sites for primers and probes for real time-PCR for *gag* PVL in these carriers did not show consistent polymorphism of the proviral DNA (data not shown). This may be because there is high diversity of proviral DNA sequence in the *gag* region of HTLV-1 and it was not possible to prepare cloning primers to work for all of them.

The other two (C20 and 21) showed low ratios not only of 5′LTR-*gag* PVL/*pX* PVL but also of *gag* PVL/*pX* PVL. Our previous study showed that they had high PVLs and clonal expansion of HTLV-1 infected cells with defective provirus.[19] We could not identify the type of defective provirus in the previous study. In our study, however, we found provirus lacking 5′LTR and its internal flanking region existed in these carriers.

In our study, the provirus with deficiency and/or polymorphism of the *gag* region was commonly found in asymptomatic HTLV-1 carriers. Few carriers had provirus lacking 5′LTR and its flanking sequence. Carriers with provirus with deficiency and/or polymorphism of the *gag* region were found frequently among asymptomatic carriers with high PVLs. These infected cells may not express certain HTLV-1 proteins. This change may make it possible for the HTLV-1 infected cells to avoid attack by cytotoxic T-lymphocytes.[33] Therefore, there is a possibility that provirus with deficiency and/or polymorphism of HTLV-1 provirus contributes to the survival of HTLV-1 infected cells. Indeed, our previous study showed that C1, 20 and 21 had clonal expansion of HTLV-1 infected cells.[19]

Low *gag* PVL/*pX* PVL ratio was found to be associated with maternal infection. The reason carriers with maternal infection have a greater number of HTLV-1 infected cells harboring provirus with deficiency and/or polymorphism of the *gag* region was not clear in our study. The replication of HTLV-1 infected cells in long-term infected carriers may account for this. Alternatively, a low level of new cell to cell infection *in vivo* can contribute to the creation of deficiency and/or polymorphism in proviral genome.

Maternal infection has been considered to be a risk factor for the development of ATL in asymptomatic carriers. However, there has been no method to identify infection route in the absence of information on family HTLV-1 status. The results of our study suggest the possibility that *gag* PVL/*pX* PVL ratio can be used as a tool to differentiate the infection routes of asymptomatic HTLV-1 carriers. Due to the fact that only a small number of HTLV-1 carriers with known infectious routes were analyzed in our study, further study with a larger number of subjects is necessary.

A major limitation of our study is that the subjects were elderly individuals, whose median age was 67 years old. The average age at onset of ATL was reported as 60 years.[34] Therefore, it is not clear whether the same result would be obtained from an analysis of younger HTLV-1 asymptomatic carriers. In addition, carriers with low *pX* PVL (less than 1 copy/100 PBMCs) were not provided for the analysis of deficiency and/or polymorphism of HTLV-1 proviral sequence because of technical limitations. Further analysis of carriers with low PVLs using improved methodology is necessary.

In conclusion, our study showed that *pX* PVL in carriers with maternal infection was significantly higher than that in carriers with spousal infection. Low *gag* PVL/*pX* PVL ratio reflecting deficiency and/or polymorphism in proviral genome was associated with high PVLs and maternal infection. These data suggest that development of ATL in carriers with maternal infection may be due in part to high PVL, which can be related to provirus with deficiency and/or polymorphism in proviral genome. In addition, *gag* PVL/*pX* PVL ratio has potential for use as a tool to differentiate infection routes of asymptomatic HTLV-1 carriers. Further study is necessary to clarify the mechanism of deficiency and/or polymorphism in HTLV-1 proviral genome and its implications in ATL development.

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derma, leucomelanoderma, or generalized leucoderma and leucotrichia.[4]

The biological mechanisms leading to cGVHD are not well understood. Most investigators now consider cGVHD to be a disease of immune dysregulation that involves donor-derived immune cells and host cell populations and tissues. This process is probably initiated by donor-derived T cells, and is both alloreactive (directed against the recipient's histocompatibility antigens) and autoreactive (directed against antigens present in both the donor and the recipient).[5,6] Leucoderma in GVHD has been suggested possibly to be related to antimelanocyte antibodies[3] or vitiligo-like T cell-mediated cytotoxic destruction of melanocytes.[4]

Cytotoxic T cells have been implicated in the pathomechanism of vitiligo based on observational studies by Yee *et al.*,[7] who reported vitiligo after immunotherapy of melanoma. Their work showed evidence that immunotherapy-induced cytotoxic T lymphocytes reactive to melanocytic differentiation antigens (e.g. MART-1), when coadministered with interleukin-2, could mediate melanocyte destruction by direct cytotoxicity after cognate antigen recognition. This pathomechanism was also suggested by Jacobsohn *et al.*[4] to account for the case of a 14-year-old boy who presented with rapid-onset total leucoderma, associated with GVHD.

Skin-directed therapy in cGVHD includes topical agents (corticosteroids, tacrolimus) and phototherapy [ultraviolet (UV) A1, oral 8-methoxypsoralen and UVA, narrow-band UVB]. However, areas of leucoderma show limited clinical improvement.[8] Autologous cellular grafting procedures have been used in patients with stable leucoderma associated with segmental vitiligo, piebaldism and halo naevus with repigmentation rates of 80–100% in nonacral sites,[9] and also in cases of postinflammatory depigmentation due to burns or discoid lupus erythematosus.[10] The successful repigmentation demonstrated in these reports forms the basis to justify the use of this technique for treating GVHD-associated leucoderma.

This report affirms the justification. The rapid and almost complete repigmentation makes this a viable treatment modality for GVHD-associated leucoderma that has achieved clinical stability.

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High levels of activation-induced cytidine deaminase expression in adult T-cell leukaemia/lymphoma

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Madam, Adult T-cell leukaemia/lymphoma (ATLL) is a malignancy of mature CD4+ T cells caused by a human T-cell leukaemia virus type I (HTLV-1).[1] This endemic haematological neoplasm is prevalent in southern Japan and develops in 1–5% of individuals infected with HTLV-1 after more than two decades of viral persistence. ATLL malignant T cells are usually positive for CD4 and CD25. Cutaneous involvement is seen in up to 50% of patients with ATLL, and various skin eruptions, such as erythroderma, tumours, nodules and papules, are observed. Recently, we showed that the type of skin eruptions is an independent and important prognostic indicator for ATLL.[2]

Activation-induced cytidine deaminase (AICDA) is a member of the cytidine deaminase family that acts as an editor of DNA and RNA, and is essential for somatic hypermutation and class-switch recombination in immunoglobulin genes.[3] Several lines of evidence have revealed that inappropriate expression of AICDA acts as a genomic mutator that contributes to

tumorigenesis.[4] AICDA is highly expressed in malignant cancers, such as gastric cancer and hepatocellular carcinoma, after *Helicobacter pylori* or hepatitis virus infection.[5] In a patient with ATLL, we found that peripheral CD4+ CD25+ cells highly expressed AICDA and contained a mutation of the tumour suppressor gene, *TP53*. This finding led us to investigate the AICDA expression in peripheral blood and skin-infiltrating ATLL cells in 18 patients with ATLL.

A 70-year-old woman visited our hospital with a 5-year history of erythema and papules (patient 3 in Table 1). On examination, the patient had painful, indurated, erythematous lesions on the buttocks (Fig. 1a) and a scaly erythematous eruption on the chest. Laboratory analysis demonstrated an increased number of atypical lymphocytes (33%) with a normal leucocyte count, a high titre of antibodies to HTLV-1 and a high level of soluble interleukin-2 receptor (4240·1 IU mL^{-1}). Southern blot analysis revealed a monoclonal HTLV-1 proviral DNA integration. On flow cytometry, the frequency of CD4+ CD25+ cells (45·1%) was increased in peripheral blood mononuclear cells (PBMC). Based on clinical and laboratory findings, the patient was diagnosed with ATLL.

To explore the expression of AICDA in the skin of this patient, we performed an immunohistochemical study using an antihuman AICDA antibody (Zymed Laboratories, Carlsbad, CA, U.S.A.). AICDA was expressed by atypical lymphocytes infiltrating the dermis (Fig. 1b). AICDA expression was not detected in skin and lymph node samples of patients with mycosis fungoides or Sézary syndrome, or normal control samples.

We analysed the expression level of *AICDA* (previously known as *AID*) mRNA from PBMC of 18 patients with ATLL, four HTLV-1 carriers, two patients with mycosis fungoides, one patient with Sézary syndrome and seven normal subjects using the real-time polymerase chain reaction 7300 system (Applied Biosystems, Foster City, CA, U.S.A.). Detailed information on the patients is summarized in Table 1. The expression level of *AICDA* mRNA in the PBMC of patients with ATLL was well correlated with the frequency of CD4+ CD25+ cells that contained ATLL malignant T cells, while *AICDA* expression was not detected in the PBMC of four HTLV-1 carriers, two patients with mycosis fungoides, one patient with Sézary syndrome and the seven normal subjects (Fig. 1c).

To ascertain whether *AICDA* mRNA was expressed by CD4+ CD25+ cells in patient 3, we separated CD4+ CD25+ cells, CD4+ CD25− cells and CD4− cells from the patient's PBMC by immunomagnetic sorting with a CD4+ CD25+ T-cell isolation kit (Miltenyi Biotec, Bergisch Gladbach, Germany). *AICDA* mRNA was expressed most highly in CD4+ CD25+ cell fractions (Fig. 1d). We further searched for a mutation of the tumour suppressor gene, *TP53*, in CD4+ CD25+ cells of the patient. Sequence analysis revealed a mutation of the *TP53* gene, c.184G>A (p.E62K) in CD4+ CD25+ cells, but not in CD4− cells (Fig. 1e).

Recently, the Tax protein of HTLV-1 has been reported to induce AICDA expression.[7] Our study suggests that the

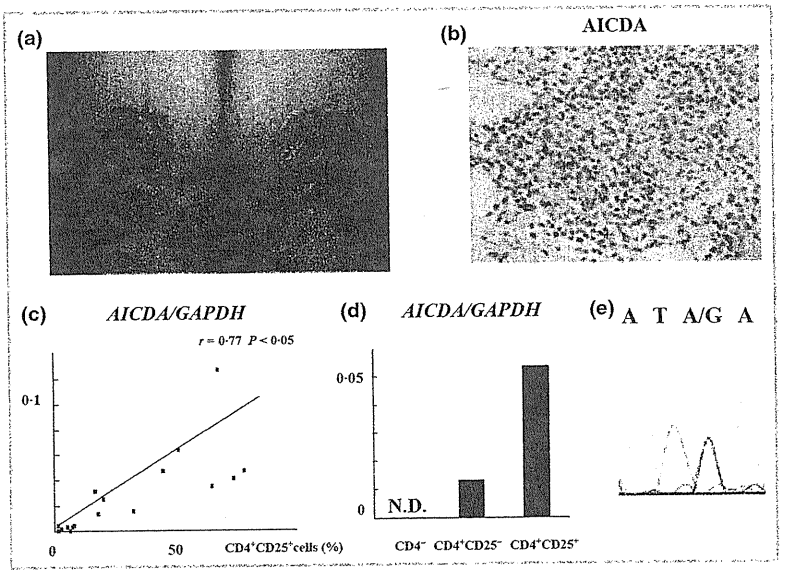

Fig 1. (a) Clinical manifestation of patient 3. Painful erythema on the buttocks. (b) Activation-induced cytidine deaminase (AICDA) expression by atypical lymphocytes in the dermis of patient 3. (c) Real-time polymerase chain reaction analysis of *AICDA* mRNA expression levels by peripheral blood mononuclear cells of patients with adult T-cell leukaemia/lymphoma. The expression levels of *AICDA* and glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) were examined using 20× Assays-on-Demand Gene Expression Assay Mix (Hs00221068_m1 and Hs00266705_g1, respectively; Applied Biosystems) with a 7000 system (Applied Biosystems) according to the manufacturer's instructions. The *AICDA* mRNA expression level was well correlated with the percentages of CD4+ CD25+ cells. (d) High expression of *AICDA* mRNA by CD4+ CD25+ T cells from patient 3. N.D., not detected. (e) A missense mutation c.184G>A (p.E62K) of the *TP53* gene in CD4+ CD25+ T cells of patient 3.

Table 1 Details of the patients with adult T-cell leukaemia/lymphoma (ATLL) and human T-cell leukaemia virus type I carriers enrolled in this study. T staging of patients with ATLL was evaluated according to the article by Sawada *et al.*,[2] and clinical types of each case were based on Shimoyama's classification[6]

Patient	Age (years)	Sex	Stage	Type	CD4+ CD25+ cells (%)	LDH (IU mL^{-1})	Ca (mg dL^{-1})	Soluble IL-2 receptor (IU mL^{-1})	Outcome	*AICDA*/*GAPDH* PBMC	CD4−	CD4+ CD25−	CD4+ CD25+	Skin
1	76	F	T3	C	68·2	213	10·3	11 412	Dead	0·12				0·15
2	73	M	T3	C	51·8	165	9·0	1352	Alive	0·063				
3	70	F	T3	S	45·1	192	9·1	4240·1	Alive	0·046	ND	0·013	0·054	
4	76	F	T3	S	74·2	810	9·8	27 097	Alive	0·040				0·087
5	70	M	T3	A	78·7	311	8·3	27 020	Dead	0·034				0·00010
6	77	F	T4	C	65·3	225	8·6	UC	Alive	0·030	ND	0·00069	0·059	
7	83	M	T3	C	20·4	326	9·4	5555	Alive	0·025				0·068
8	91	M	T3	C	33·0	336	8·6	2813	Dead	0·015	ND	0·000017	0·029	
9	91	M	T3	S	18·2	214	9·4	1186	Alive	0·013				0·053
10	53	M	T2	C	16·9	288	9·9	2793	Alive	0·0043				
11	47	F	T2	S	8·2	407	9·5	1479	Alive	0·0042	ND	0·014	0·054	
12	65	M	T2	S	7·5	264	8·7	3752	Alive	0·0029				0·018
13	53	F	T1	S	5·2	218	9·8	2996	Alive	0·0027	ND	ND	0·012	
14	67	M	T1	S	2·8	232	8·6	606	Alive	0·0016	ND	0·0021	0·0084	
15	66	M	T1	S	1·6	1131	9·8	8219	Alive	0·00028	ND	0·00063	0·019	
16	82	M	T1	S	6·4	327	9·3	UC	Alive	0·000052				
17	45	F	T4	A	1·7	190	UC	2814	Alive	0·0000013				
18	89	F	T3	C	5·7	192	8·4	2005	Alive	ND				
19	69	F	Carrier		UC	177	UC	UC	Alive	ND	ND	ND	ND	
20	59	F	Carrier		UC	175	UC	UC	Alive	ND	ND	ND	ND	
21	56	M	Carrier		UC	268	9·1	UC	Alive	ND	ND	ND	ND	
22	86	M	Carrier		UC	247	9·8	UC	Alive	ND	ND	ND	ND	

LDH, lactate dehydrogenase; IL, interleukin; PBMC, peripheral blood mononuclear cells; C, chronic type; S, smouldering type; A, acute type; UC, not checked; ND, not detected.

highly expressed AICDA, possibly induced by HTLV-1 infection, leads to mutations of tumour suppressor genes and resultant neoplastic change in CD4+ CD25+ T cells of the patients. AICDA may play a role in the progression from carrier state to overt ATLL. Furthermore, the three patients (patients 1, 5 and 8) who had high levels of *AICDA* expression, died of ATLL during this study period. The expression level of AICDA in PBMC can be one of the prognostic indicators in patients with ATLL.

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